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Large Sequential Outbreaks Caused by Influenza A (H3N2) and B Viruses in an Institution for the Mentally Handicapped

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During the mixed epidemic caused by influenza A (H3N2) and B in the 1992–1993 season in Japan, large sequential outbreaks occurred in an institution for mentally handicapped people where none of the residents or staff members had been immunized. During the influenza A outbreak (A/Beijing/32/92-like strain) in January, 37.0% of the residents (85/230) and 31.4% of the staff (75/239) had an influenza-like illness. During the influenza B outbreak (B/Panama/45/90- and B/Beijing/184/93-like strain) in late February, 59.0% of the residents and 24.3% of the staff had an influenza-like illness. As many as 25.2% of the residents had two episodes of influenza-like illness during the season, as opposed to only 5.4% of the staff members. Mixed epidemics probably have a severe impact on institutionalized high-risk people, adversely affecting them almost twice as much as influenza epidemics caused by a single virus.

KEY WORDS: influenza virus, nosocomial infection, amantadine

INTRODUCTION

In recent years, Japan has often experienced large mixed influenza epidemics caused by influenza A (H3N2) and B viruses, as in 1989–1990, 1992–1993, and 1994–1995 [Sugaya et al., 1992, 1994]. The patterns of these epidemics have been similar. An epidemic resulting from influenza A (H3N2) occurred first in December and peaked in January and was followed by an influenza B virus epidemic, which continued until March. Thus, the total epidemic period lasted 3–4 months, more than twice as long as usual epidemics caused by a single influenza virus [Gross et al., 1988]. Consequently, the number of influenza patients reported increased to the level of a large epidemic, even though the scale of the individual influenza A or B epidemic was small or moderate. Such mixed epidemics have occasionally been reported [Paul et al., 1988] but their characteristics in influenza epidemiology have not been fully noticed, and the impact on high risk-people has not been reported.

During the mixed epidemic of 1992–1993, large sequential outbreaks caused by influenza A (H3N2) and B viruses occurred in an institution for mentally and physically handicapped people where no residents and staff members had been immunized before the epidemic. Moreover, the influenza B outbreak in the institution was shown to be caused serially by two variants of influenza B virus. This paper describes the impact of the mixed epidemic on the residents and staff members in the institution.

SUBJECTS AND METHODS

Institution

The site of the outbreak was a large residential facility for mentally and physically handicapped people in Tokyo, Japan. The residents (total 230) lived on six wards, to which they had been assigned by degree of disability; three wards (A–C) housed 141 severely impaired residents (most with a diagnosis of cerebral palsy) who required full-time medical care for chronic underlying conditions; ward D was a short-term facility (usually several weeks), housing 9 residents, regardless of degree of disability. Two other wards (E and F) housed 80 residents who were moderately handicapped (most with a diagnosis of mental retardation). The wards were completely separate, and residents on different wards never participated in the same activities, such as walks or exercise programs during the outbreak.

No residents had received influenza vaccine before the epidemic. Influenza vaccine had never been offered to the residents of this institution.

The mean age of the residents on ward A was 19.9 years; it was 35.0 years on ward B, 8.3 years on ward C, and 14.0 years on ward D. Ward E was for males, and

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their mean age was 32.0 years, and ward F was for females, and their mean age was 36.4 years.

There were 239 staff members at this institution (mean age 34.0 years, range 18–65 years), including 199 nurses and nurse assistants on each ward, 36 rehabilitation program personnel, and 4 physicians. Rehabilitation personnel and physicians made a round of the wards every day, and they were the only staff members who circulated between wards. All staff members shared a common dining room and locker room, and about one-third of them lived in the institution's dormitory. No staff members had received influenza vaccine before the epidemic, and there had been no influenza vaccination program for staff members in the institution.

Phylogenetic Analysis

An evolutionary tree was constructed from all of the positions of the nucleotide sequences of the hemagglutinin gene, as described previously [Nei and Gojobori, 1986; Kanegae et al., 1990].

Clinical Influenza

Residents and staff members who had a temperature of ≥38.5°C with cough and/or coryza were defined as having clinical influenza.

Diagnosis of Influenza Virus Infection

To the extent possible, throat swabs and acute and convalescent serum specimens were obtained from the patients with clinical influenza. The diagnosis of influenza virus infection was established when a virus was isolated and/or the individual exhibited a fourfold or greater increase in hemagglutination inhibition (HI) antibody titer to influenza A (H3N2) or B viruses.

HI tests were carried out with A/Beijing/352/89 (H3N2) and B/Panama/45/90-like strain (B/Bangkok/163/90) as antigens. They were the same strains as were in the vaccine that season. Specimens for influenza virus isolation were collected with throat swabs. Samples were inoculated into Madin-Darby canine kidney cells. For statistical analysis, the χ^2 test was used.

RESULTS

During the 1992–1993 winter season, a severe mixed influenza epidemic occurred in Japan. Influenza A (H3N2) virus was the main epidemic virus from December, 1992, to the end of January, 1993. By February, 1993, outbreaks of influenza B virus had been reported in many areas of the country. The influenza B epidemic peaked in the mid-February and had run its course by the end of February.

The epidemic viruses were identified and confirmed at the National Institute of Health, Japan, as influenza A/Kitakyushu/159/93 (H3N2) (A/Beijing/32/92-like strain) and B/Bangkok/163/90 (B/Panama/45/90-like strain). In addition, sporadic outbreaks of influenza B virus were reported in some areas of the country from the beginning of March through April, and the drifted strain, B/Mie/1/93 (B/Beijing/184/93-like strain), was isolated.

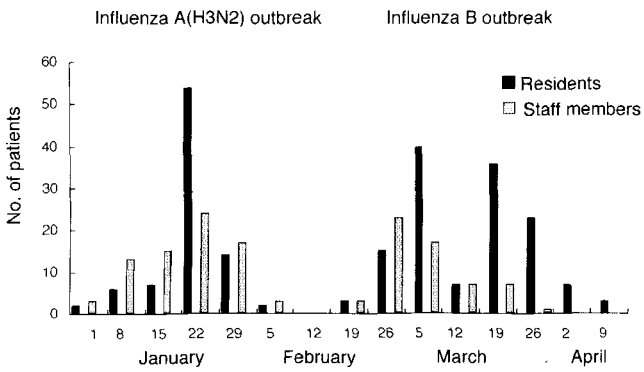

Fig. 1. Residents and staff members with clinical influenza. Eighty-five residents (85/230; 37.0%) and 75 staff members (75/239; 31.4%) had clinical influenza during the influenza A (H3N2) outbreak (from January 7 through February 6), and 134 residents (134/227; 59.0%) and 58 staff members (58/239; 24.3%) had clinical influenza during the influenza B outbreak (from February 24 to April 10).

Outbreak of Influenza A (H3N2) at the Institution

Patients with clinical influenza first occurred in the institution at the beginning of January, 1993 (Fig. 1). The first patient with serologically confirmed influenza A (H3N2) virus infection was a resident of ward D and became febrile on January 7. In the first half of January, clinical influenza was more common among the staff than among the residents. Towards the end of January, the numbers of affected patients increased markedly, mainly residents of wards A and B. The outbreak then rapidly disappeared at the beginning of February. The last patient with virologically confirmed influenza A (H3N2) infection developed a febrile illness on February 6. Therefore, the influenza A (H3N2) epidemic at the institution was considered to have extended from January 7 to February 6. A total of 85 residents (85/230; 37.0%) and 75 staff members (75/239; 31.4%) had clinical influenza during the influenza A (H3N2) outbreak. The incidences of illness of the residents vs. the staff members were not statistically different ($P > 0.1$).

Paired sera were obtained from 69 of the 85 residents with clinical influenza during the influenza A (H3N2) outbreak. Fourfold or greater rises in HI antibody against A/Beijing/352/89 (H3N2) were demonstrated in 43 of these 69 patients. No significant rises in HI antibody against B/Panama/45/90-like strain were shown in the 69 patients. One of the eleven throat swabs obtained from ill residents yielded an influenza A (H3N2) virus, A/Beijing/32/92. In total, 44 (51.8%) of the 85 residents with clinical influenza were confirmed to have influenza A (H3N2) virus infection. No staff members underwent HI testing or virus isolation.

The resident attack rate on ward A, where all 50 residents started receiving amantadine chloride (100 mg/day) on January 27, was 44.0% (Table I). On ward C, where 24 of the 41 residents were treated with amantadine chloride (50 mg/day) starting on January 23, it was 24.4%. The attack rates on ward B (92.0%) and ward D

TABLE I. Incidence of Illness Among Residents and Staff Members*

	Ward											
	A		B		C		D		E		F	
	R*	S*	R	S	R	S	R	S	R	S	R	S
Mean age (years)	19	31	35	33	8	32	14	44	32	37	36	32
A (H3N2) outbreak incidence of illness (%)	44.0	37.5	92.0	29.3	24.4	26.8	77.8	64.3	0	3.1	0	6.5
B outbreak incidence of illness (%)	82.0	20.0	83.7	7.3	5.0	9.8	0	0	80.0	59.4	45.0	45.2

*R, residents; S, staff members. Residents on wards A and C received amantadine chloride (100 mg/day) during the influenza A (H3N2) outbreak. No staff members were given amantadine chloride.

(77.8%), where amantadine prophylaxis was not performed, were much higher. No patients with clinical influenza were reported on wards E and F, because most residents had returned home for the New Year holidays and stayed there until the outbreak subsided.

Many cases of clinical influenza were reported among the staff members, except on wards E and F. The attack rates were as follows: 37.5% on ward A, 29.3% on ward B, 26.8% on ward C, and 64.3% on ward D (Table I). The rehabilitation program personnel and physicians had high attack rates, 61.1% and 75.0%, respectively. No staff members were given amantadine chloride.

During the outbreak, 21 (24.7%) of the 85 residents with clinical influenza developed pneumonia, and three of them died. Among the staff members, 8 (10.7%) of the 75 with clinical influenza had bronchitis.

Outbreak of Influenza B in the Institution

An outbreak of clinical influenza appeared again in the institution in the latter half of February (Fig. 1), mainly on wards E and F, where no outbreak of influenza A (H3N2) virus had occurred among the residents. The first patient with serologically confirmed influenza B virus infection was a resident on ward E who contracted the illness on February 24. Patients with clinical influenza gradually increased, peaking in the beginning of March. Clinical influenza was more common among the staff members than among the residents in the early phase of the outbreak. In the second week of March, the number of patients decreased, and the outbreak seemed to be ending. However, during the following week (the third week of March), the number of those with clinical influenza increased markedly again, this time mainly on wards A and B. The outbreak ended in the second week of April. The last patient with serologically confirmed influenza B developed a febrile illness on April 10. Therefore, residents and staff members who had clinical influenza from February 24 to April 10 were considered to have influenza B virus infection. A total of 134 of the 227 residents (59.0%) and 58 of the 239 staff members (24.3%) had clinical influenza during the influenza B outbreak. The difference between the incidence of illness among the residents vs. the staff members was statistically significant ($P < 0.01$).

Paired sera were obtained from 75 of the 134 residents with clinical influenza. Fourfold or greater rises of HI antibody were demonstrated in 62 of the 75, and 26 of the 109 throat swabs obtained from ill residents yielded influenza B viruses, 16 of the 26 being from those with significant rises in HI antibody. In total, 72 (53.7%) of the 134 residents with clinical influenza were confirmed virologically to have influenza B virus infection. One of four throat swabs obtained from the staff members yielded influenza B virus, but the HI test was not performed.

The resident attack rates reached 80% or more on wards A (82.0%), B (83.7%), and E (80.0%) but reached only 45.0% on ward F (Table I). No outbreaks were observed on ward C or D.

A high percentage of staff members on wards E (59.4%) and F (45.2%) had clinical influenza (Table I). The attack rates on the other wards are as follows: 20.0% on ward A, 7.3% on ward B, 9.8% on ward C, and 0% on ward D. The rehabilitation program personnel and physicians had relatively high attack rates, 25.1% and 25.0%, respectively.

Thirteen (9.7%) of the 134 residents with clinical influenza during the influenza B outbreak had pneumonia. One of them, a patient with cerebral palsy, died. Five (8.6%) of the 58 staff members with clinical influenza had bronchitis.

Two Variants of Influenza B Virus

The outbreak of influenza B virus was caused sequentially by two variants, B/Panama/45/90 and B/Beijing/184/93 (Table II). B/Beijing/184/93 is the drifted strain of B/Panama/45/90. Two epidemic peaks, one for each influenza B virus, are clearly indicated in Figure 1.

The first peak of the outbreak was caused by B/Panama/45/90. The outbreak was epidemic mainly on wards E and F from the end of February to the middle of March. Nine strains of B/Panama/45/90 were isolated from the residents of wards E and F.

The second peak was caused by B/Beijing/184/93. The outbreak was epidemic on wards A and B from the latter half of March to the beginning of April. Seventeen strains of B/Beijing/184/93 were isolated from the residents of wards A and B. The occurrence of clinical influenza continued throughout the entire influenza B outbreak only on ward B.

Most staff members had clinical influenza during the outbreak of B/Panama/45/90 (Fig. 1); 51 of the 58 staff members with clinical influenza (87.9%) developed a febrile illness before March 19. B/Panama/45/90 was isolated from one of them on March 9.

None of the residents or staff members had two epi-

TABLE II. Antigenic Analysis of Influenza B Viruses Isolated in the Institution*

Test viruses	Date	Specific ferret-infected serum		
		B/Yamagata/16/88	B/Bangkok/163/90 (B/Panama/45/90)	B/Mie/1/93 (B/Beijing/184/93)
Reference strains				
B/Yamagata/16/88	—	2,048	256	64
B/Bangkok/163/90	—	128	512	32
B/Mie/1/93	—	128	128	1,024
B isolates, Bangkok lineage				
TS-13, TS-31[a]	March 3	512	512	128
TS-43, TS-50, TS-66[a]	March 9	512	512	128
B isolates, Mie lineage				
TS-96,	March 25	256	128	512
TS-103, TS-111, TS-116[a]	March 30	256	128	512
TS-127[a]	April 7	256	128	512

*Values represent the reciprocal of the final dilution that inhibited hemagglutination of the test antigens. Bangkok and Mie lineages represent antigenic characteristics identical to B/Bangkok/163/90 (B/Panama/45/90-like strain) and B/Mie/1/93 (B/Beijing/184/93-like strain).
[a]These isolates were further characterized by phylogenetic analysis.

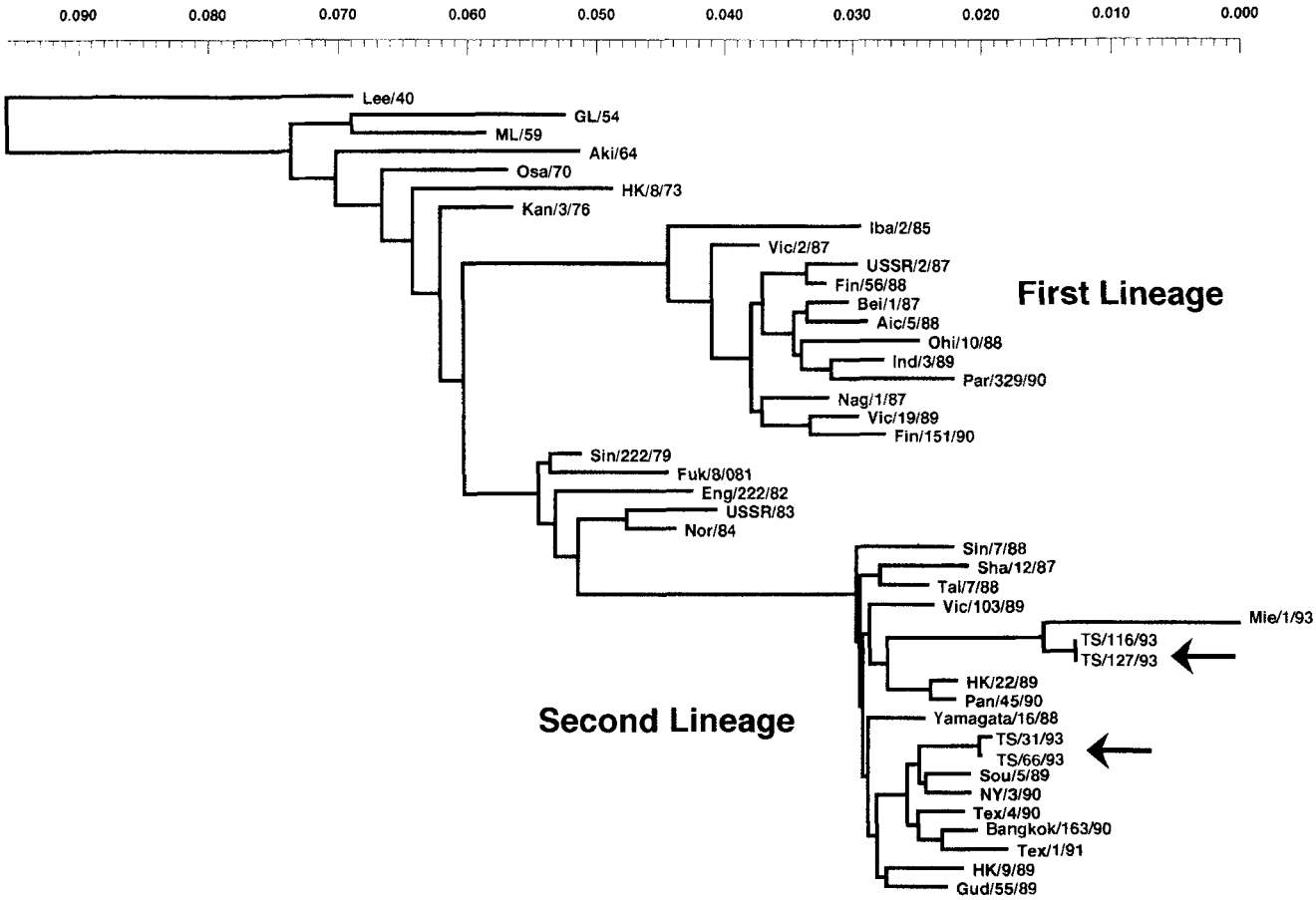

Fig. 2. Evolutionary interrelationship of influenza B viruses based on calculated mutational distances between entire HA1 domains. Genomic distance was estimated on the basis of the number of silent substitutions. The length of each branch was estimated by the principle of minimum evolution.

sodes of clinical influenza throughout the entire period of the influenza B outbreak. Moreover, none was found to be sequentially infected with both influenza B variants by virus isolation.

As is shown in Figure 2, influenza B viruses have evolved into two lineages since 1987. The first lineage includes Iba/2/85, Vic/2/87, and Fin/151/90 viruses, and the second lineage includes Sin/7/88, Yamagata/16/88, and Bangkok/163/90 (B/Panama/45/90-like strain) viruses. The viruses belonging to the second lineage are

further divided into three minor branch clusters. Two strains, TS/31/93 and TS/66/93, isolated during the first peak of the influenza B outbreak are in the third branch cluster, including B/Bangkok/163/90 (B/Panama/45/90-like strain). TS/116/93 and TS/127/93 isolated during the second peak of the influenza B outbreak, on the other hand, belong to the second branch cluster, which includes B/Mie/1/93 virus (B/Beijing/184/93-like strain). This evolutionary tree shows clearly that two different variants of influenza B virus appeared sequentially in the institution.

Clinical Influenza During the Influenza A (H3N2) and B Outbreaks

As many as 25.2% of the residents (58/230) experienced two episodes of clinical influenza during the outbreaks of influenza A (H3N2) and influenza B. Most of them were the residents on wards A and B (19 on ward A, 38 on ward B, and 1 on ward C). Infection by both influenza viruses was confirmed by the HI test and/or virus isolation in 13 of the 58 (22.4%). On the other hand, only 5.4% of staff members (13/239) had two episodes of clinical influenza during the same period. The incidence of illness in the residents was significantly higher than that in the staff members ($P < 0.01$). No clinical influenza was detected in 30.0% of the residents (69/230) and 49.4% of the staff members (118/239) during the mixed influenza epidemic.

DISCUSSION

To our knowledge, this is the first report of large sequential outbreaks of influenza caused by influenza A (H3N2) and B viruses in a single institution during the same season. Perhaps institutionalized high-risk people frequently become infected by both influenza viruses when a mixed influenza epidemic occurs. In this study, as many as 25.2% of the residents had two episodes of influenza-like illness, compared to only 5.4% of the staff members ($P < 0.01$). The results of this study suggest that an immunization program should be vigorously carried out for high-risk people, especially when a mixed influenza epidemic is anticipated.

Presumably both A/Beijing/32/92 and B/Panama/45/90 viruses were introduced into the institution by the staff members, because influenza is usually introduced into closed environments by medical personnel [Heilman and La, 1990]. In fact, during both influenza outbreaks, most of the staff had clinical influenza in the early phase of the outbreaks. Moreover, it is almost certain that the spread of influenza across the wards was caused by the staff members, especially rehabilitation program personnel and physicians, because the residents in each ward were kept in strict isolation during the outbreaks. Influenza immunization has not been recommended for medical personnel in Japan [Dowdle et al., 1980; Oya and Nerone, 1986]. These findings strongly support the proposition that medical personnel caring for high-risk people should be immunized annually [Arden et al., 1988; Hoffman and Dixon, 1977; Pachucki et al., 1989].

A marked difference between the incidence of illness among the residents and among the staff members was shown during the influenza B outbreak (59.0% vs. 24.3%; $P < 0.01$), especially in wards A and B (Table I). Although the residents of both wards were adults, their infection history for influenza B virus was probably limited compared to that of the staff members, because most of them had been institutionalized since childhood. As a result, they had a high incidence of infection by influenza B virus.

The incidences of illness among the residents and staff members were equivalent during the influenza A (H3N2) outbreak (37.0% vs. 31.4%; $P > 0.1$), although the epidemic strain of influenza A (H3N2), A/Beijing/32/92, had marked drift [Sugaya et al., 1994]. Amantadine prophylaxis was probably effective for the residents on wards A and C during the influenza A (H3N2) outbreak, lowering the incidence of illness among the residents.

The results of our study show that the residents with clinical influenza during the influenza A outbreak were more likely to develop pneumonia than those with clinical influenza during the influenza B outbreak (24.7% vs. 9.7%; $P < 0.01$), supporting the view that adults are generally less susceptible to severe infection with influenza B virus [Glezen et al., 1980; Kendal, 1987; Foy et al., 1979].

This study underscores the potential of influenza B virus to cause explosive outbreaks in a closed environment, not only among children [Klein et al., 1976] but also among adults with underlying illnesses and elderly people [Hall et al., 1981]. It is especially interesting that the emergence of the drifted strain, B/Beijing/184/93, in the later phase of the influenza B outbreak caused extension of the outbreak in the institution. To our knowledge, two different variants of influenza B have never been isolated in one institutional outbreak. Because several strains of B/Beijing/184/93 were isolated in Tokyo during the 1992–1993 season, it is appropriate to assume that the drifted strain was also introduced into the institution by the staff. However, the possibility exists that B/Beijing/184/93 emerged inside the institution as a result of the preceding outbreak of B/Panama/45/90 by accumulation of single-point mutations [Kanegae et al., 1990].

In this study, about half of the residents with clinical influenza during each outbreak were virologically confirmed to have influenza A (H3N2) and B infection (51.8% vs. 53.7%). No staff members with clinical influenza were virologically confirmed to have influenza virus infection, except for one with influenza B. Although the possible concurrent occurrences of outbreaks of acute respiratory infections caused by other agents were not excluded [Gross et al., 1988], the majority of the illnesses were probably caused by influenza viruses.

When a mixed epidemic from influenza A (H3N2) and B viruses occurs, each influenza virus often appears sequentially, and the total epidemic period is markedly prolonged. Mixed epidemics probably have a severe impact on high-risk people in institutions, adversely affect-

ing them almost twice as much as an influenza epidemic caused by a single virus.

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